IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

10x GENOMICS, INC.,	)	
	)	
Plaintiff,	)	
	)	C.A. No. 19-862-CFC-SRF
v.	)	
	)	
CELSEE, INC.,	)	
	)	
Defendant.	)	
	)	

CELSEE, INC.'S MEMORANDUM IN SUPPORT OF ITS SECOND MOTION FOR SUMMARY JUDGMENT (INVALIDITY OF THE BRENNER PATENTS UNDER 35 U.S.C. §112)

Dated: February 5, 2021

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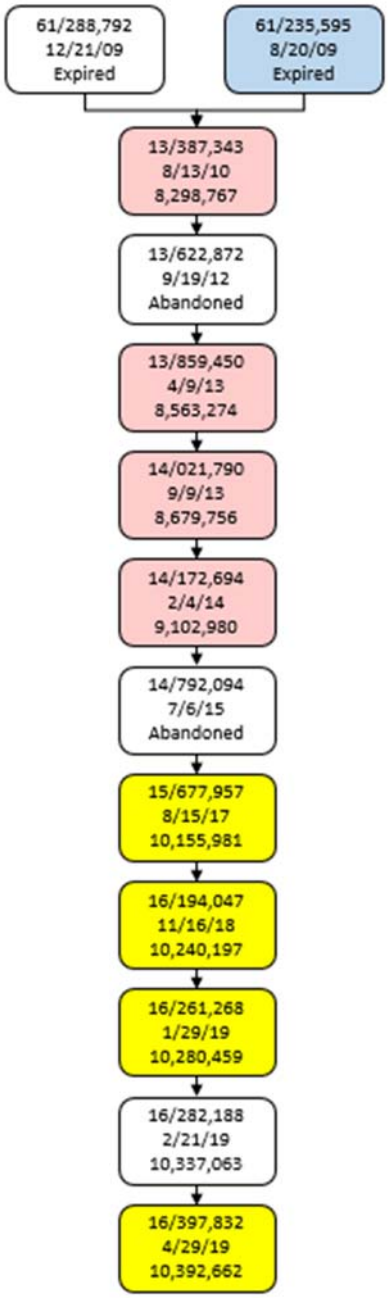
Celsee submits this Memorandum in support of its motion for summary judgment of invalidity for lack of written description of all claims of the "Brenner Patents" asserted by 10x: U.S. Patent Nos. 10,155,981 ("'981"), claims 1 and 4; 10,240,197 ("'197"), claims 1, 10, 20, 23-24; 10,280,459 (the "'459"), claims 1 and 4; and 10,392,662 ("'662"), claims 1, 3-5 and 11.

SUMMARY OF ARGUMENT

The Brenner Patent specification concerns the "reflex process," which allows researchers to sequence large DNA fragments. During claim construction, 10x successfully urged this Court to reject Celsee's argument that the claims, read in light of the specification, are directed to an application of the reflex process. The Court adopted 10x's broad interpretation of the claims as encompassing methods and compositions related to multiplexed single-cell tagging and analysis—subject matter not disclosed in the specification. 10x must now face the consequences: its claims are invalid for lack of written description.

BACKGROUND[1]

I. Prosecution of the Brenner Patents



As shown in the figure, the Brenner Patents (yellow highlighted) share a common specification and trace their lineage back to provisional patent application No. 61,235/595 (the "'595 Provisional," blue highlighted). SF2-1; SF2-2. The '595 Provisional was filed in 2009 by UK company Population Genetics Technologies ("PGT"). SF2-2; SF2-3. PGT later filed Application No. 13/387,343, its first utility application claiming priority to the '595 Provisional, and subsequently filed several continuation applications (indicated with black arrows). PGT's prosecution efforts led to the issuance of four U.S. patents—all related to the "reflex process" (pink highlighted). Exs.F-I.

[1] This background is for the Court's convenience. For the facts material to this Motion, see accompanying Statement of Facts ("SF2"). Citations to exhibits ("Ex.") refer to exhibits attached thereto.

In 2016, after launching its single-cell analysis product, 10x bought those four patents from PGT, as well as the right to control prosecution of future applications. Soon thereafter, 10x began pursuing claims directed to single-cell analysis using a two-part oligonucleotide tag—subject matter that was never claimed as an invention by PGT.

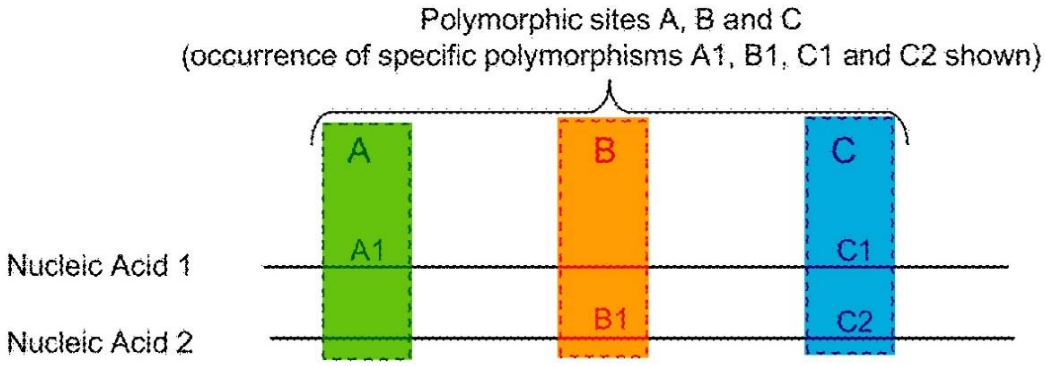
II. The Reflex Process[2]

In the specification's "Background of the Invention," the PGT inventors identified the problem with then-existing nucleic acid sequencing technology that they set out to solve with the disclosed invention: researchers wanted to sequence nucleic acid fragments that "are longer than the lengths that can be sequenced by a particular technology." Ex.A[981], 1:32-36. If the large "parent" fragments were further fragmented into smaller "daughter" pieces before sequencing to address this length limitation, then researchers could not link the sequences of daughter fragments that came from the same parent. As a result, researchers could not link a "sequence change" on one daughter fragment with a sequence change on a sister fragment (*i.e.*, a fragment from the same parent). *Id.*, 1:39-43.

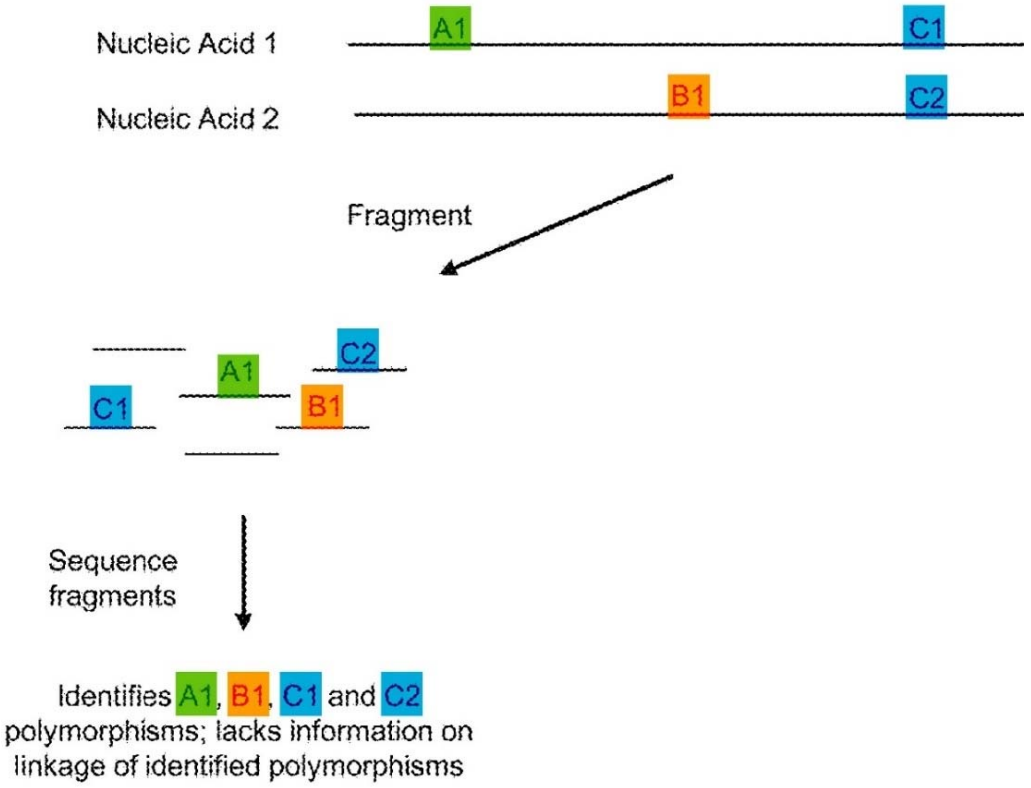
Figure 5 of the specification (below, color added) illustrates how the reflex process works. Figure 5's top schematic depicts two long polynucleotides, Nucleic

[2] For additional description of the reflex process, *see* Ex.J, p.6-12.

Acid 1 and Nucleic Acid 2, each having three regions of interest (A, B, and C, respectively) where sequence changes ("polymorphisms") may be present. *Id.*, 2:23-34 (figure legend). Nucleic Acid 1 contains polymorphism A1 within region A and polymorphism C1 within region C; Nucleic Acid 2 contains polymorphism B1 within region B and polymorphism C2 within region C.

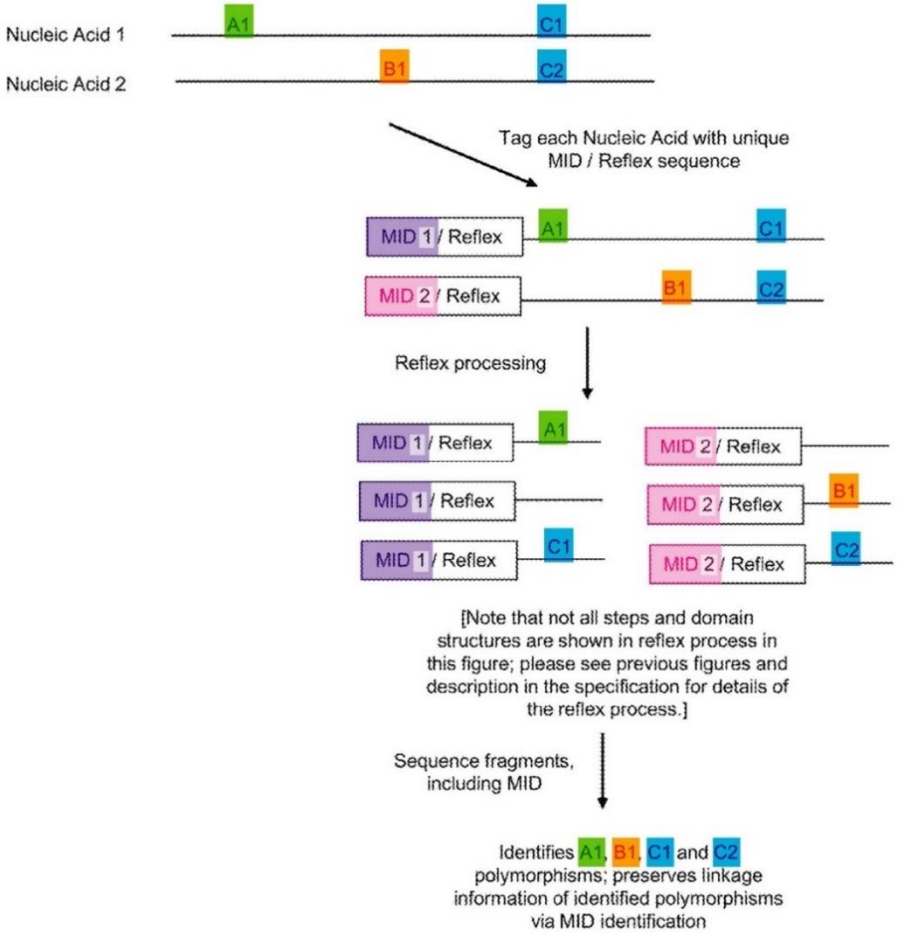


The left side of Figure 5 (below, color added) illustrates a traditional fragmentation-based approach for sequencing long polynucleotides in which the reflex process is not used. *Id.* The long original nucleic acids are fragmented into pieces small enough for sequencing. While sequencing these smaller fragments allows for the identification of the presence of the polymorphisms within the sample, there is no way of knowing which polymorphisms came from Nucleic Acid 1 and which came from Nucleic Acid 2.



The right side of Figure 5 (below, color added) illustrates how the reflex process allows polymorphisms in a given fragment to be linked back to their parent polynucleotide. *Id*. Distinct tags, referred to as a "Multiplex Identifiers" or "MIDs" in the specification and designated "MID1" and "MID2" in Figure 5, are attached to the end of Nucleic Acid 1 and Nucleic Acid 2 along with a "reflex sequence." Then, reflex processing is performed, during which each of the regions of interest (A, B, and C) is moved into proximity with the attached MID/reflex tag. The reflex process generates three tagged polynucleotides from each of Nucleic Acid 1 and Nucleic Acid 2. Each tagged polynucleotide includes a MID that identifies its parent polynucleotide (*e.g.*, polynucleotides from Nucleic Acid 1 are tagged with

MID1; polynucleotides from Nucleic Acid 2 are tagged with MID2). The tagged polynucleotides are then sequenced and the MID is used to link the sequence of each polynucleotide, including any polymorphism in it, back to its parent polynucleotide. Because A1 and C1 are tagged with MID1, they are known to have originated from Nucleic Acid 1; because B1 and C2 are tagged with MID2, they are known to have originated from Nucleic Acid 2.



Each of the 13 figures and all 5 of the examples in the specification concern the reflex process. SF2-4.

III. Multiplexed Single-Cell Analysis

Under this Court's Claim Construction Order (D.I. 154), the Brenner Method Patent claims do not require the "reflex process" and instead relate to multiplexed single-cell analysis, which is not discussed in the specification.

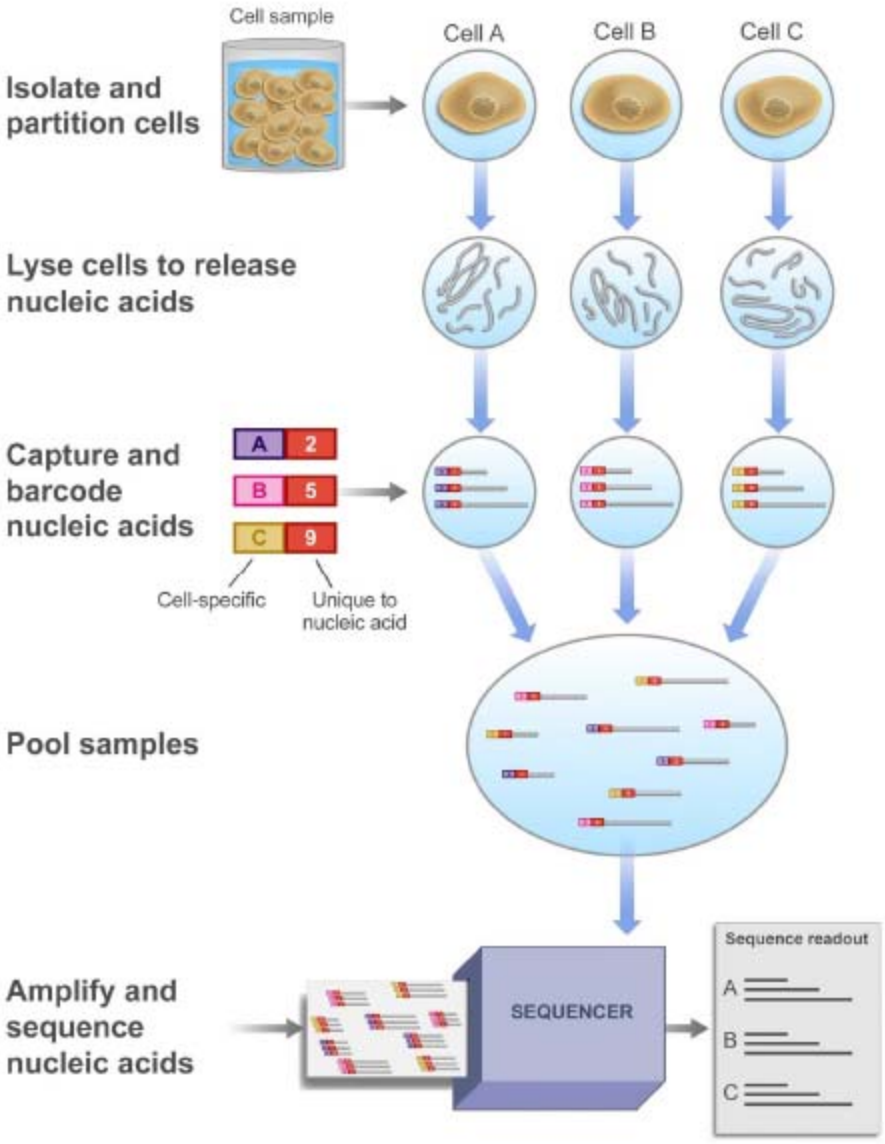
Multiplexed single-cell analysis leverages modern sequencing technology to enable large-scale sequencing of nucleic acids from single cells in a biological sample. "Multiplexing" refers to the ability to pool multiple biological samples for sequencing by attaching nucleic acid barcodes (sometimes referred to as "multiplex identifiers" or "MIDs") to the polynucleotides being sequenced. The process can be used to study DNA or RNA in a cell.

The workflow of a typical single-cell sequencing experiment encompasses the following steps, depicted below. First, individual cells are isolated from one another, or "partitioned." Second, the individual cells' membranes are ruptured ("lysed") to release the cells' nucleic acids.

Third, the released nucleic acids are "tagged" with tags comprising "barcodes." This tag is a synthetic DNA sequence and may consist of multiple components. Typically, one component is a "cell-specific barcode." Nucleic acids originating from a given cell are tagged with the same cell-specific barcode which allows nucleic acids that originate from one cell to be distinguished from those that originate from a different cell. A tag may also contain another barcode known as a

"unique molecule identifier" ("UMI"). This barcode should be different for each polynucleotide to be sequenced, even those that originate from the same cell. This is accomplished by ensuring that tags within a given partition have UMIs different from each other.

Fourth, once the barcoding is complete, the tagged nucleic acids are pooled together in a single tube. The pool of molecules can subsequently be "amplified" using PCR, a routine technique that creates many copies of the input molecules. This amplification ensures there is sufficient amount of material to analyze with a sequencer. After sequencing, each sequence can be traced back to an individual cell, and, if a UMI was used, to an individual molecule.



IV. The Asserted Claims

All asserted claims of the ’981, ’197, and ’459 Patents (the “Brenner Method Patents”) relate to methods of multiplexed single-cell tagging and analysis, and require the performance of a series of steps including:

(1) providing a sample comprising a plurality of single cells;

(2) generating a plurality of tagged polynucleotides comprising a sequence from a sample, and a MID comprising a first tag sequence associated with the single cell from which the sample polynucleotide is derived (*i.e.*, a cell-specific tag) and a second tag sequence distinguishing the sample polynucleotide from other sample polynucleotides from the single cell (*i.e.*, a polynucleotide-specific tag);

(3) sequencing the tagged polynucleotides; and

(4) using the tagged sequences to correlate the sequences with a sample cell and a sample polynucleotide or to count sample polynucleotides from a cell. SF2-5 to SF2-8.

The asserted claims of the ’662 Patent relate to compositions for multiplexed single-cell tagging and analysis. The claimed compositions comprise a plurality of beads covalently attached to a plurality of oligonucleotide tags wherein the oligonucleotide tag comprises a cell-specific tag and a polynucleotide-specific tag. SF2-9.

ARGUMENT

I. THE ASSERTED CLAIMS ARE INVALID FOR LACK OF WRITTEN DESCRIPTION.

The purpose of §112’s written description requirement is two-fold. First, it serves as a quid pro quo “in which the public is given ‘meaningful disclosure in exchange for being excluded from practicing the invention for a limited period of

time.'" *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 920, 922 (Fed. Cir. 2004). Second, it "operates as a timing mechanism to ensure fair play in the presentation of claims after the original filing date and to guard against manipulation of that process by the patent applicant." *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1307 (Fed. Cir. 2008); *see Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1561 (Fed Cir. 1991) ("Adequate description of the invention guards against the inventor's overreaching by insisting that he recount his invention in such detail that his future claims can be determined to be encompassed within his original creation.").

To satisfy written description, the specification must "clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *Ariad Pharms., Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). In other words, the specification itself must show that "the inventor actually invented the invention claimed" and must "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Id.*

The question is not whether a claimed invention is an obvious variant of an embodiment described in the specification, or whether one skilled in the art might be able to construct the claimed invention. *Id.* at 1352; *ICU Med., Inc. v. Alaris Med. Sys., Inc.*, 558 F.3d 1368, 1378-79 (Fed. Cir. 2009); *Lockwood v. Am.*

Airlines, 107 F.3d 1565, 1572 (Fed. Cir. 1997). In other words, the written description requirement does not focus on what a person of ordinary skill could do, but rather on what the inventors themselves ***did*** do. The specification must describe the invention as broadly as it is claimed, to demonstrate that the inventors actually invented the full scope of the claimed invention by the time they filed the application. *See Ariad*, 598 F.3d at 1351-52.

Summary judgment of invalidity for lack of written description is appropriate where the fact-finder could not reasonably find the claimed inventions are adequately disclosed in the specification. *Atl. Research Mktg. Sys., Inc. v. Troy*, 659 F.3d 1345, 1353 (Fed. Cir. 2011); *Univ. of Rochester*, 358 F.3d at 917 (Fed. Cir. 2004).

A. The specification does not describe the claimed methods.

To determine whether there is adequate description to support a claim, the Court must analyze the claim "as an integrated whole rather than as a collection of independent limitations." *Novozymes* A/S v. *Dupont Nutrition BioSciences APS*, 723 F.3d 1336, 1349 (Fed. Cir. 2013).

It is undisputed that the specific single-cell analysis methods recited in the asserted claims of the Brenner Method Patents are not described as an integrated whole in the specification. SF2-10. Instead, 10x cobbles together a definition of a multiplex identifier (MID) (*e.g.*, Ex.K ¶¶1457-1458, 1465-1466) with a passing

mention of the possible use of single cells in the reflex process (*e.g.*, Ex.K ¶¶1456, 1463) and certain isolated downstream applications of the reflex process (*e.g.*, Ex.K ¶¶1459, 1461, 1464, 1467-1469) in a manner never suggested in the specification to arrive at the purported §112 support for an invention never contemplated by the PGT inventors.

There is no disclosure in the specification of generating a plurality of tagged polynucleotides from single cells as required by all claims of the Brenner Method Patents. The ***only*** time it mentions single cells is as part of a laundry list of potential sources of polynucleotide samples that can be used in the reflex process. SF2-11. None of the basic steps of multiplex single-cell analysis are described (*e.g.*, partitioning single cells, lysis, tagging polynucleotides, and pooling and amplifying tagged polynucleotides). Ex.L ¶¶511-520. Instead, the entirety of the specification, including all figures and examples, focuses on what the PGT inventors viewed as their invention: performing the reflex process on cells in bulk. *Boston Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1364 (Fed. Cir. 2011) ("the lack of any disclosure of examples may be considered when determining whether the claimed invention is adequately described.").

Nor is there any disclosure of a multiplex identifier sequence comprising a cell-specific tag and a molecule-specific tag as required by all asserted claims of the Brenner Method Patents. The specification contains no description whatsoever

of the use of these dual-tag MIDs in a single-cell analysis method. Instead, the specification describes the use of MID tags ***in the reflex reaction*** to ensure that a barcode denoting the identity of a parent molecule (a source-specific tag) can be placed in close proximity to multiple regions of interest on that molecule. SF2-12.

Finally, there is no disclosure of counting nucleic acids in a sample required by the '197 and '459 claims. Ex.B[197], Ex.C[459]. The only reference to counting methods in the entire specification is in a passage related to the reflex process that ineffectively incorporates by reference a patent disclosing a method for counting molecules. SF2-13. *See Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000).

The claims of the Brenner Method Patents are a textbook example of what the written description doctrine was intended to prevent. *Agilent Techs., Inc. v. Affymetrix, Inc.*, 567 F.3d 1366, 1379 (Fed. Cir. 2009) (§112 "prohibits new matter from entering into claim amendments, particularly during the continuation process."). The specification describes one method—the reflex process—but patent claims, filed seven years after the original application by a company that acquired the patent family, are directed to another—multiplexed single-cell analysis. *See* Ex.L. These claims should be held invalid for lack of written description.

B. The specification does not describe the beads claimed in the '662 Patent.

10x does not dispute that there is no disclosure of beads covalently attached to oligonucleotide tags, an element of all asserted '662 claims. Instead, 10x's expert argues that "[c]ovalent bonds, and how to form them, are a fundamental building block in basic chemistry" so a POSA "would understand that the inventors possessed such a composition." Ex.K ¶1447. Even if covalent bonds were well known in the art, this would, at best, make the covalent attachment of oligonucleotide tags to beads ***obvious***, but not adequately described. *See Regents of Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566-67 (Fed. Cir. 1997) ("an applicant complies with the written description requirement 'by describing the invention, with all its claimed limitations, not that which makes it obvious'"). Thus, the lack of any disclosure in specification of a bead covalently attached to oligonucleotide tags is fatal to the validity of the asserted '662 claims.

Even if the specification disclosed a bead covalently attached to a polynucleotide tag (which it does not), it is undisputed that the specification does not describe a bead covalently attached to an oligonucleotide tag which comprises a cell-specific tag and a molecule-specific tag as required by the asserted claims. SF2-14. The '662 claims lack written description support for this additional reason.

Dated: February 5, 2021

Respectfully submitted,

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CERTIFICATION OF COMPLIANCE

The foregoing document complies with the type-volume limitation of this Court's March 2, 2020 form Scheduling Order For All Cases where Infringement is Alleged. The text of this brief, including footnotes, was prepared in Times New Roman, 14 point. According to the word processing system used to prepare it, the brief contains 2,563 words, excluding the case caption, signature block, table of contents and table of authorities.

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Dated: February 5, 2021